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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/507,452	04/12/2005	Shishan Ji	1547/3	1381
25297 7590 08/03/2010 JENKINS, WILSON, TAYLOR & HUNT, P. A. Suite 1200 UNIVERSITY TOWER 3100 TOWER BLVD., DURHAM, NC 27707				
EXAMINER				
WHEELER, THURMAN MICHAEL				
ART UNIT		PAPER NUMBER		
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MAIL DATE		DELIVERY MODE		
08/03/2010		PAPER		

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/507,452

Applicant(s)

JI ET AL.

Examiner

Thurman Wheeler

Art Unit

1619

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 23 April 2010.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-59 is/are pending in the application.
- 4a) Of the above claim(s) 5, 6, 16, 17, 25-30, 38, 39, 43-56, 58 and 59 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-4, 7-9, 13, 15, 18-24, 36, 37, 40-42 and 57 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

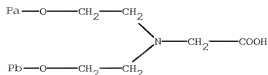
Claims 1-59 are pending in instant application

1. Applicants' election without traverse of Group I, claims 1-5, 7-9, 13, 15-30, 36-49, 52, 53, 57 and 58 in the reply filed on 4/23/2010 is acknowledged.

$$\begin{array}{c} \text{Pa} \text{---} \text{X}_1 \\ \text{Pb} \text{---} \text{X}_2 \end{array} \quad \text{N} \text{---} (\text{CHR}_i)_j \text{---} \text{F} \quad (1)$$
$$\begin{array}{c} m \text{ PEG-O-CH}_2\text{CH}_2 \\ m \text{ PEG-O-CH}_2 \\ \text{O} \\ \parallel \\ \text{N}-\text{CH}-\text{C}-\text{OH} \\ | \\ \text{R}_1 \end{array}$$

Applicants also elected the conjugate wherein the drug species is a protein.

An alternate species of formula (I) of claim 1 was selected by the examiner for further prosecution of instant application, wherein Pa and Pb are each a polyethylene glycol; j is 1; R_i is H; X₁ is (CH₂)_n, wherein n is 2; X₂ is (CH₂)_n, wherein n is 2; and F is a carboxyl group (shown below):



Claims 5, 6, 16, 17, 25-30, 38, 39, 43-56, 58 and 59 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected claims, there being no allowable generic or linking claim.

Claim 14 is cancelled.

The restriction requirement is still deemed proper and is therefore made FINAL.

Herein, claims 1-4, 7-9, 13, 15 (protein), 18-24, 36, 37 (protein), 40-42 and 57 are for further prosecution.

Claim Rejections - 35 USC § 102

2. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

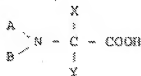
A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Instant claims 1-4, 7-9 and 22-24 are rejected under 35 U.S.C. 102(b) as anticipated by Marumo et al (USP 3855156).

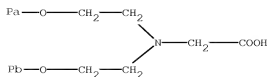
Applicants' claimed invention is directed towards Y-shape branched hydrophilic polymer derivatives and conjugates of the derivatives and drug molecules, especially proteins.

Marumo teaches chemical compounds represented by the general formula (shown below):



In particular, Marumo teaches compounds, wherein A and B represent $-(\text{CH}_2\text{CHR}'\text{O})_q\text{H}$, and R' is a hydrogen or a $-\text{CH}_3$ group and q is integer from 0 to 50 (col.1, lns.5-60), which corresponds

to the alternate elected species as shown below (Y-branched polyethylene glycol (PEG) glycine):



Therefore, claims 1-4, 7-9 and 22-24 are anticipated by the teachings of Marumo.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining differences between the prior art and claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered

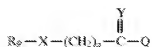
therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-4, 7-9, 13, 15, 18-24, 36, 37, 40-42 and 57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Marumo et al (USP 3855156) in view of Greenwald et al (USP 5824701) and Karasiewicz et al (USP 5382657).

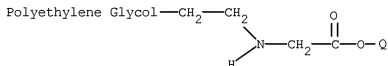
Claims 1-4, 7-9 and 22-24 are described in the 102 rejection over Marumo.

However, the Marumo reference does not embody conjugates of the chemical compounds and drug molecules, especially proteins.

Greenwald teaches modifications of the anti-tumor agent taxol (paclitaxel) in order to enhance water solubility and/or improve therapeutic activity when compared to the unmodified paclitaxel or taxane compositions (col.3, lns.53-58). In particular, Greenwald teaches modifications to taxol that include the addition of polyethylene glycol (PEG) amino acid derivatives according to the following general formula (as shown below) (col.9, lns.5-10):



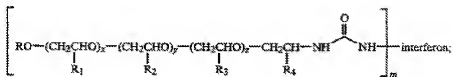
In particular, when R_9 (col.8, lns.10-11) is a polyethylene glycol, X is NH, n is 1 (col.7, line 40), and Q is a group capable of being displaced by a nucleophilic reagent, then a polyethylene glycol (PEG) glycine substituent e.g. mPEG-NH-CH₂-CO₂Q that can be added to taxol is provided in accordance with the teachings of Greenwald (as shown below).



Further, Greenwald teaches polyethylene glycols molecular weights of from about 20,000 to about 50,000 (col.8, lns.20-27).

Greenwald teaches that the modified taxoid can be included in one or more suitable pharmaceutical compositions for administration to mammals. The pharmaceutical compositions can be in the form of a solution, suspension, tablet, capsule or the like, prepared according to methods well known in the art. It is also contemplated that administration of such compositions may be by the oral and/or parenteral routes depending upon the needs of the artisan (col.12, lns.35-64).

Karasiewicz 5382657 teaches PEG-Interferon conjugates having the following structure as shown below:



Karasiewicz teaches interferon-PEG conjugates with unique linkers which connect an amino group in the interferon (IFN) to polyethylene glycol (PEG). Karasiewicz teaches physiologically active conjugates, wherein R is lower alkyl; R₁, R₂, R₃, R₄ are hydrogen and at least one is lower alkyl; m is a number up to the number of accessible amino groups in the protein and x, y and z are selected from any combination of numbers such that the conjugate has at least a portion of the biological activity of the protein which forms the conjugate (col.2, lns.24-31).

Karasiewicz teaches that the interferon (IFN) conjugates of formula, as shown above, are produced by condensing activated PEG where a terminal hydroxy (e.g. (RO(-CH₂CH₂O)_xNHCO₂H) has been replaced by an activated linker. These reagents can then react with one or more of the free amino groups in the IFN (col.2, lns.59-64; also see claim 12).

It would have been obvious to one skilled in the art at the time of the invention to use a polyethylene glycol glycine compound as taught by Marumo to functionalize a protein, e.g. interferon, in order to increase its pharmaceutical utility as

taught by Karasiewicz. One of ordinary skill in the art would have recognized the advantage of modifying a poorly water soluble compound with hydrophilic polymers such as polyethylene glycol glycine in order to enhance its water solubility as taught by Greenwald. Further, one skilled in the art would have recognized the benefit of using a Y-branched polyethylene glycol glycine as taught by Marumo having doubled the amount of polyethylene glycol groups to increase the amount of water soluble substituents surrounding the protein, which would further increase its solubility and pharmacological half life as a medicament.

One skilled in the art at the time of the invention would have had a reasonable amount of expectation of success to provide Y-shape branched hydrophilic polymer derivatives and conjugates of the derivatives and drug molecules, especially proteins, by following the teachings of Marumo, Greenwald and Karasiewicz, as a whole.

Accordingly, the claimed invention of instant claims 1-4, 7-9, 13, 15, 18-24, 36, 37, 40-42 and 57 were prima facie obvious to one skilled in the art at the time of the invention was made especially in the absence of evidence to the contrary.

4. A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claims 6-9 of instant application are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 6-9 of copending Application No. 12781173. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

5. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or

improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-3, 13 and 15-21 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 2, 6-9, 13, and 15-21 of copending Application No. 12781173 ('173 herein).

Although the conflicting claims are not identical, they are not patentably distinct from each other because claim 6 of '173 consists of Y-branched polyethylene glycol derivatives that are a species that anticipates the Y-branched hydrophilic polymer derivatives of claim 1 (genus claim) of instant application. Further, it would be prima facie obvious to provide conjugates formed from the Y-branched hydrophilic polymer derivatives of claim 1, because the conjugates formed from the Y-branched polyethylene glycol derivatives of claim 6 of '173 are a species of the conjugates that can be formed from the derivatives of claim 1 of instant application.

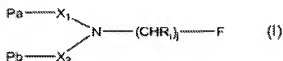
This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusions

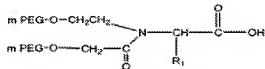
6. All claims are rejected.

Allowable Subject Matter

7. Applicants' elected species is allowable (shown below).



wherein Pa and Pb are each a polyethylene glycol; j is 1; R_i is H; X₁ is (CH₂)_n wherein n is 2; X₂ is (CH₂)_nCO wherein n is 1; and F is a carboxyl group. See Instant Specification, Example 5, page 18, lines 1-17 and in Figure 3 (shown below):



8. Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Thurman Wheeler whose telephone number is (571)270-1307. The examiner can normally be reached on Monday-Friday, 9:00 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached on 571-272-0871. The fax phone number for the

organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Tracy Vivlemore/
Primary Examiner, Art Unit 1635